UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,144	09/27/2004	Kurt Berlin	82309	6722

23685 7590 05/21/2008
KRIEGSMAN & KRIEGSMAN
30 TURNPIKE ROAD, SUITE 9
SOUTHBOROUGH, MA 01772

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
05/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,144	BERLIN, KURT	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/5/2008 has been entered.

Claim Status

The response has amended claim 1. Claims 12-15 are withdrawn.

The 112-2nd paragraph rejection of claims 1-11 has been withdrawn due to amendment of the claims.

An action on the merits of claims 1-11 follows.

Sequence Compliance

The application fails to comply with CFR 1.821(d), which states:

(d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, page 20 lines 21-22, contains a nucleic acid sequence. Applicant is required to check the rest of the disclosure for any other nucleic acid or protein

sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification and sequence listing must be amended to bring it into sequence compliance. **For any response to this office action to be fully compliant, the response has to bring the application in compliance with sequence rules.**

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-6, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010).

Genomic methylation pattern is interpreted to include tissue specific methylation patterns.

The amendment to the claims to recite hemimethylation requires the presence of a methylated and non-methylated strands.

Lopez et al teaches the amplification of genomic DNA by PCR in the presence of a thermostable DNA methyltransferase (see figure 1and page 17, lines 26-28) (claim 1) and amplification by single strand displacement amplification and methylation with a DNA methyltransferase (see page 18, line 10-16) for detection. PCR and single strand

displacement amplification are interpreted as steps A-C of claim 1. The strands synthesized by chain extension or single strand displacement contain the methylated parent strand and synthesized strand, which is not methylated and thus are hemimethylated. Lopez teaches ^{3}H-s-adenosyl methionine as a methyl donor with a detectable label (see page 4, line 2) (claim 4 and 5). Lopez et al further teaches the use of anchored PCR primers on a solid matrix to create ordered maps (see page 21 lines 2-4) (claim 6). Lopez et al teaches the treatment of amplified targets with a restriction enzyme capable of distinguishing methylated and non-methylated cytosines (see page 32, lines25-29).

Lopez et al does not teach the use of DNA methyltransferase that preserves methylation status of genomic DNA (claim1). Lopez et al does not teach the use of DNMT1 a maintenance methyltransferase (claims 2 and 3).

However, Pradhan et al teaches the use of DNMT1 as a methyltransferase (see abstract). Pradhan teaches maintenance methylation "ensures propagation of tissue specific methylation patterns during development" (see page 33002, first column text, lines 8-10). Pradhan teaches that DNMT1 has a higher reaction velocity for hemimethylated DNA substrates (see page 3302, 2nd column, last paragraph). Pradhan thus teaches DNMT1 is a maintenance methyltransferase ensures propagation of specific methylation patterns. Pradhan further teaches cytosine methylation is important in embryonic development, carcinogenesis and genetic disease (see page 33002, 1st column of text lines 1-5). Pradhan thus teaches maintenance methylation and the

methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease.

Therefore it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the DNMT1 methyltransferase taught by Pradhan as the methyltransferase in Lopez's method because Pradhan teaches DNMT1 is a maintenance methyltransferase that ensures propagation of methylation patterns. The ordinary artisan would be motivated to use the DNMT1 of Pradhan with Lopez method of methylating amplified DNA because Pradhan maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease. The artisan would have a reasonable expectation of success as they are merely replacing a one methyltransferase for another.

Response to Arguments

The response of 3/5/2008 asserts in the first line of page 7 that the present invention teaches, "a method for use in METHYLATION analysis." This is noted, however the invention as claimed is drawn to a method of amplifying genomic DNA is a manner in which methylation status is maintained.

The response further asserts on the top of page 8, the PCR amplification of Lopez "erases all existing methylation information." This argument has been thoroughly reviewed but is not considered persuasive as PCR amplification does not result in a loss of methylation information, as the methylation on the genomic DNA is still intact, not erased. Thus the assertion that the method of Lopez "erases all existing methylation information" is incorrect and thus not persuasive.

The response further asserts the method of detecting would be unreliable if partially methylated DNA is produced. This argument has been thoroughly reviewed but is not considered persuasive as Lopez does not teach that the genomic methylation status is lost. Lopez is being used to merely teach that methods of amplifying genomic DNA by the use of PCR which requires heating, cooling and primer extension were known.

The response further asserts, "Lopez teaches a completely different problem in a completely different technology." This argument has been thoroughly reviewed but is not considered persuasive as Lopez is drawn to a method of amplifying genomic DNA and analyzing methylation status by use of a methyl transferase. The instant invention is drawn to the use of amplifying genomic DNA using a methyltransferase. Thus the methods while directed to slightly different outcomes both use amplification of genomic DNA and a methyltransferase. The difference between the Lopez and the instant method is that the claimed method requires the use of a methylation sensitive methyltransferase, such as DNMT1 taught by Pradhan, which will maintain methylation status of the genomic DNA. Thus the difference is the substitution of a single reagent. It is noted that simply replacing the methyltransferase of Lopez with the DNMT1 and using DNMT1 would result in an amplification of a plurality of different of nucleic acids with their methylation pattern intact as each initially amplified strand would result in the production of a complement in which methylation was maintained.

However, it would have also been obvious to the ordinary artisan to add a DNMT1 after each heating, cooling and primer extension cycle as Pradhan teaches the

protein is labile and thus subject to degradation at moderate temperatures (see page 33005, 1st column, 1st full paragraph).

4. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Shatkin et al (US Patent 6312926).

The teachings of Lopez and Pradhan are set forth above. Lopez and Pradhan do not teach the methyltransferase immobilized on a solid support.

However, Shatkin et al teaches the use of hMET (methyl transferase) immobilized on protein G beads for washing assays (see column 24, lines 3-12).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase taught by Shatkin, because Shatkin teaches immobilization allows washing of assays. The ordinary artisan would be motivated to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase or polymerases as taught by Shatkin, because Shatkin teaches immobilization allows washing of assay and detection of protein interactions.

Response to Arguments

The response of 3/5/2008 asserts that Shatkin et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

5. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Stemple et al (WO/2000/53805).

The teachings of Lopez and Pradhan are set forth above. Lopez and Pradhan do not teach the polymerase immobilized on a solid support.

However, Stemple teaches the immobilization of a polymerase on a solid support (see page 3 lines 14-15). Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously (See page 7, lines 25-26).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilizing a polymerases as taught by Stemple, because Stemple teaches

immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously. The ordinary artisan would be motivated to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously.

Reponse to Arguments

The response of 3/5/2008 that Stemple et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying genomic DNA wherein the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

6. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claims 1-6, 9, and 10 above, and further in view of Gonzalgo et al (US Patent 6251594).

The teachings of Lopez and Pradhan are set forth above. Lopez and Pradhan do not teach the use of bisulphate solution to distinguish methylation status of cytosine bases.

However, Gonzalgo et al teach the use of bisulphite to distinguish methylated and unmethylated cytosines (column 7, lines 5-6). Gonzalgo teaches the use of bisulphite is quantitative, does not use restriction enzymes, and allows multiplexing (see column 7, lines 7-10).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez and Pradhan's method of amplifying genomic DNA while maintaining and distinguishing genomic methylation patterns by use bisulphite solutions taught by Gonzalgo, because Gonazalgo teaches the use of bisulphate is quantitative, does not use restriction enzymes, and allows multiplexing. The ordinary artisan would be motivated to improve Lopez and Pradhan's method because, the use of bisulphite is quantitative, does not use restriction enzymes, and allows multiplexing. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Reponse to Arguments

The response of 3/5/2008 that Gonzalgo et al does not cure all of the deficiencies of Lopez in view of Pradhan, as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Lopez in view of Pradhan does render the instant claims obvious as the combination would result in a method of amplifying by PCR genomic DNA wherein

the methylation status of the genomic DNA is maintained. The response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634